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(71) Applicant *(for all designated States except US)*: BRITISH BIOTECH PHARMACEUTICALS LIMITED [GB/GB]; Watlington Road, Cowley, Oxford OX4 5LY (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: MARTIN, Fionna, Mitchell [GB/GB]; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB). FLOYD, Christopher, David [GB/GB]; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB). SPAVOLD, Zoe, Marie [GB/GB]; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB). AYSCOUGH, Andrew, Paul [GB/GB]; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB). WHITTAKER, Mark [GB/GB]; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB).

(74) Agent: WALLS, Alan, J.; British Biotech Pharmaceuticals Limited, Watlington Road, Cowley, Oxford OX4 5LY (GB).

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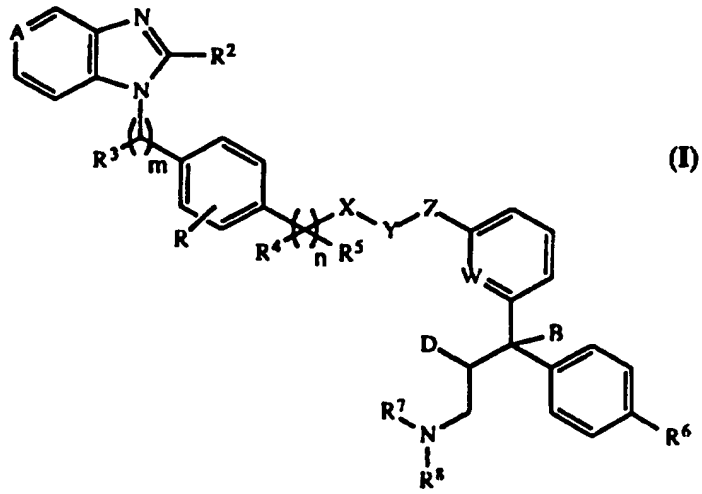
(54) Title: BENZIMIDAZOLE DERIVATIVES BEING DUAL HISTAMINE (H1) AND PLATELET ACTIVATING FACTOR (PAF) ANTAGONISTS

(57) Abstract

Compounds of formula (I), wherein the variable substituents and groups are as defined in the specification, are dual histamine (H1) and platelet activating factor (PAF) antagonists.



(I)

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BENZIMIDAZOLE DERIVATIVES BEING DUAL HISTAMINE (H1) AND PLATELET ACTIVATING FACTOR (PAF) ANTAGONISTS

This invention relates to compounds which are dual histamine (H_1) and platelet activating factor (PAF) antagonists, to therapeutic compositions containing such compounds, and to methods for their preparation.

Background to the Invention

Potent H_1 antagonists of various structural types are known, and are useful in treating the symptoms of inflammatory conditions such as allergic rhinitis, and allergic conditions of the skin, which are mediated at least in part by the release of histamine. However, in such conditions, in which histamine release plays a causative role, there may be other mechanisms at work which are not inhibited by treatment with an H_1 antagonist alone. For example PAF is released directly from cell membranes and mediates a range of potent and specific effects on target cells resulting in a wide variety of physiological responses, including hypotension, thrombocytopenia, bronchoconstriction, circulatory shock, increased vascular permeability (oedema/erythema), and accumulation of inflammatory cells in the lower airways.

There is therefore a need for agents which have dual H_1 and PAF antagonistic activity for the improved treatment of conditions mediated by histamine and PAF release. Such conditions include allergic rhinitis, sinusitis, asthma, dermatitis, psoriasis, urticaria, anaphylactic shock, conjunctivitis, pruritis, inflammatory bowel disease and colitis.

International patent application WO-A-92/03423 (British Bio-technology) discloses a series of compounds which are potent antagonists of PAF.

United States patent 2,712,020 and European patent applications EP-A-085959 and EP-A-133534 (Wellcome Foundation Ltd) disclose compounds which are potent H_1 antagonists.

International patent applications WO-A-92/14734 (Pfizer), WO-A-92/00293 (Schering), WO-A-89/10363 (Schering), WO-A-93/20080 (Schering), WO-A-93/20063 (Schering), WO-A-93/23400 (Schering), WO-A-93/02081 (Schering), WO-A-94/08581 (Toray), United States patent US5332733 (Kali-Chemie), European patent applications EP-A-515158 (Schering), EP-A-463873 (Sankyo), EP-A-549364 (Sankyo), WP-A-577957 (Uriach) and Japanese patent application published under no 4-226993 (Yoshitomi) all disclose compounds which possess both histamine (H_1) and PAF antagonist activity.

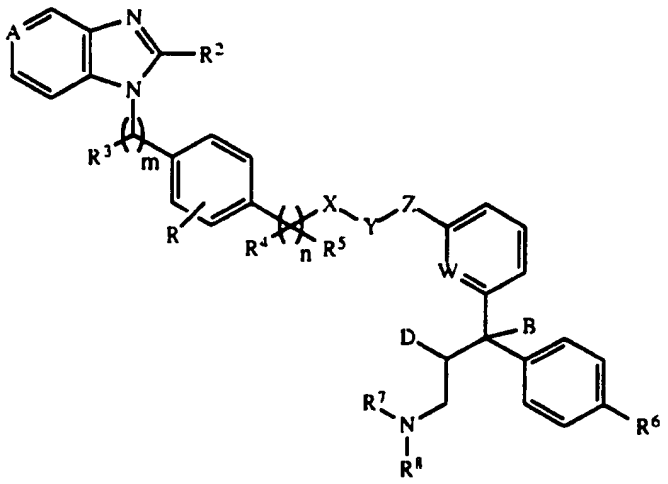
Brief Description of the Invention

One possible strategy for the design of compounds having both H_1 and PAF antagonist activity might be to couple a H_1 antagonist molecule to a PAF antagonist molecule via a flexible linker chain, with little or no structural modification of the parent H_1 and PAF antagonist molecules, such that the "H_1 fragment" of the combined molecule may bind to the H_1 receptor without distortion or interference from the "PAF fragment", and and vice versa. Disadvantages of such a strategy include the inevitable high molecular weight of the combined molecule and probable resultant poor oral bioavailability, and the difficulty of designing a linker chain which is capable of permitting the specific receptor interactions at each end of the combined molecule without substantial mutual interference.

In contrast to the above approach, the present invention makes available a class of compounds in which the structure as a whole provides a desirable balance of H_1 and PAF antagonist activity. The invention thus includes compounds having reduced molecular weight and hence bioavailability, compared with compounds consisting of separate PAF and H_1 antagonist molecules joined through a flexible linking chain.

Detailed Description of the Invention

According to the present invention there is provided a compound of formula (I)



(I)

wherein

A represents =N- or =CR^1-, wherein R^1 represents hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, halogen, -CN, -CO_2H, -CO_2(C_1-C_6 alkyl), -$CONH_2$, -CHO, -CH_2OH, -CF_3, C_1-C_6 alkoxy, C_1-C_6 alkylsulphanyl, C_1-C_6 alkylsulphinyl, C_1-C_6 alkylsulphonyl, -NH_2, -$NHCOCH_3$, or -NO_2; provided that when A represents =N- the resulting imidazo[4,5-c]pyridinyl bicyclic ring system may be optionally substituted in the 4- and/or 6-positions by methyl;

R represents hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, halogen or C_1-C_6 alkoxy;

R2 represents hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulphanyl, cyclopropyl, C_1-C_6 hydroxyalkyl, N(C_1-C_6 alkyl)$_2$, C_1-C_6 N(C_1-C_6 alkyl)$_2$ and -CF_3;

R3 represents hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -CO_2(C_1-C_6 alkyl), C_1-C_6 alkoxy, C_1-C_6 alkylsulphanyl, (C_1-C_6 alkoxy)C_1-C_6 alkyl, (C_1-C_6

alkylsulphanyl)C_1-C_6 alkyl, (phenyl)C_1-C_6 alkyl, or phenylsulphanyl;

R^4 and R^5 independently represent hydrogen or C_1-C_6 alkyl; or R^4 and R^5 taken together with the carbon atom to which they are attached form a 3-8 membered carbocyclic or heterocyclic ring;

X represents -O-, -S- or -N(R^9)- where R^9 represents hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl optionally substituted in the cycloalkyl ring with one or more C_1-C_6 alkyl groups, HOOC-(C_1-C_6 alkyl) and ester and amide derivatives thereof, hydroxy(C_1-C_6 alkyl) or C_1-C_6 alkyloxy(C_1-C_6 alkyl);

Y represents a carbonyl or sulphonyl group;

Z represents bivalent C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl group, or a single bond;

W represents -N= or -CH=;

B represents hydrogen or hydroxyl and D represents hydrogen, or B and D taken together represent -C=C-;

R^6 represents hydrogen, halogen, hydroxy, cyano, C_1-C_4 alkyl, trifluoromethyl, or C_1-C_4 alkyloxy;

R^7 and R^8 independently represent hydrogen or C_1-C_4 alkyl, or R^7 and R^8 taken together with the nitrogen atom to which they are attached form a heterocyclic ring containing 4-7 ring atoms, which ring may contain one or more heteroatoms other than the nitrogen to which R7 and R8 are attached; and

n and m independently represent 0 or 1;

or a pharmaceutically or veterinarily acceptable acid addition salt or hydrate thereof.

Hereafter in this specification the term "compound" includes "salt" or "hydrate" unless the context requires otherwise.

As used herein the term "halogen" or its abbreviation "halo" means fluoro, chloro, bromo or iodo.

As used herein the term "C_1-C_6 alkyl" refers to straight chain or branched chain hydrocarbon groups having from one to six carbon atoms. Illustrative of such alkyl groups are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl and hexyl.

As used herein the term "C_2-C_6 alkenyl" refers to straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one double bond, of either E or Z stereochemistry where applicable. This term would include for example, vinyl, 1-propenyl, 1- and 2-butenyl and 2-methyl-2-propenyl.

As used herein the term "C_2-C_6 alkynyl" refers to straight chain or branched chain hydrocarbon groups having from two to six carbon atoms and having in addition one triple bond. This term would include for example, ethynyl, 1-propynyl, 1- and 2-butynyl, 2-methyl-2-propynyl, 2-pentynyl, 3-pentynyl, 4-pentynyl, 2-hexynyl, 3-hexynyl, 4-hexynyl and 5-hexynyl.

As used herein the term "C_1-C_6 alkoxy" refers to straight chain or branched chain alkoxy groups having from one to six carbon atoms. Illustrative of such alkoxy groups are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, neopentoxy and hexoxy.

As used herein the term "C_1-C_6 alkylsulphanyl" refers to straight chain or branched

chain alkylsulphanyl groups having from one to six carbon atoms. Illustrative of such alkyl groups are methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, neopentylthio and hexylthio.

As used herein, the term "C_3-C_8 cycloalkyl" refers to an alicyclic group having from 3 to 8 carbon atoms. Illustrative of such cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In compounds of this invention, the presence of several asymmetric carbon atoms gives rise to diastereoisomers, each of which consists of two enantiomers, with the appropriate R or S stereochemistry at each chiral centre. The invention is understood to include all such diastereoisomers, their optically active enantiomers and mixtures thereof. Furthermore both E and Z isomers arising from alkenyl groups are included in the invention.

The term "pharmaceutically or veterinarily acceptable acid addition salt" refers to a salt prepared by contacting a compound of formula (I) with an acid whose anion is generally considered suitable for human or animal consumption.

Examples of pharmaceutically and/or veterinarily acceptable acid addition salts include the hydrochloride, sulphate, phosphate, acetate, propionate, lactate, maleate, succinate and tartrate salts.

Preferred compounds of formula (II) include those in which, independently or in any compatible combination:

A represents =N- ;

R represents hydrogen;

R^2 represents methyl;

R^3 represents hydrogen;

R^4 and R^5 independently represent hydrogen or C_1-C_6 alkyl, and in particular both R^4 and R^5 may represent hydrogen or R^4 may represent hydrogen and R^5 may represent methyl;

X represents -O- or -N(R^9)-, where R^9 represents hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl or C_3-C_8 cycloalkyl optionally sustituted in the cycloalkyl ring with one or more C_1-C_6 alkyl groups, and in particular R^9 may represent hydrogen, methyl or cyclohexyl;

Y represents carbonyl;

Z represents C_1-C_6 alkyl or C_2-C_6 alkenyl, in particular ethyl or E-ethenyl;

W represents -N=;

B and D taken together represent -C=C- with a further preference for E-stereochemistry;

R^6 represents methyl;

R^7 and R^8 are independently C_1-C_4 alkyl or taken together with the nitrogen atom to which they are attached form a a pyrrolidine ring; and

n and m both represent 1;

Specific preferred compounds of the invention are:

3-[6-(3-Pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylic acid 4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl ester,

N-[4-(1H-2-Methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]-3-[6-(3-

pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylamide,

N-[4-(1H-2-Methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]-3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-propionylamide,

N-[4-(1H-2-Methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]-3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-propyl)-pyridin-2-yl]-propionate,

3-[6-(3-Pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylic acid 1-[4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-phenyl]-ethylester,

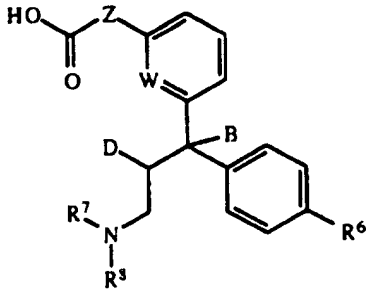
N-Methyl-N-[4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]-3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylamide,

and pharmaceutically and veterinarily acceptable acid addition salts or hydrates thereof.

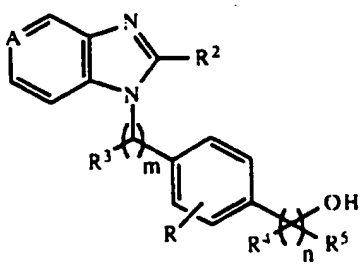
Compounds of the invention may be prepared as described below:

Route 1

Compounds of the invention in which X represents O, and Y represents CO may be prepared by esterification of an acid of formula (II) with an alcohol of formula (III).



(II)

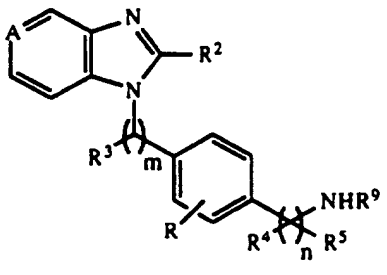


(III)

wherein R, R^2, R^3, R^4, R^5, R^6, R^7, R^8, W, Z, m, n, A, B and D are as defined in formula (I). The esterification may be facilitated by using a carbodiimide condensing agent, such as (N)-3-dimethylaminopropyl-N'-ethyl-carbodiimide. Alternatively, an activated derivative of the acid (II) may be employed for the esterification, such as the acid chloride or pentafluorophenyl ester. Dimethylaminopyridine added to the reaction mixture may facilitate the esterification reaction.

Route 2

Compounds of the invention in which X represents NR^9 and Y represents CO may be prepared by amidation of an acid of formula (II) above with an amine of formula (IV):

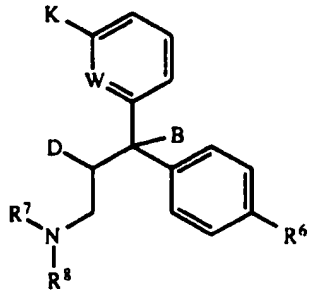


(IV)

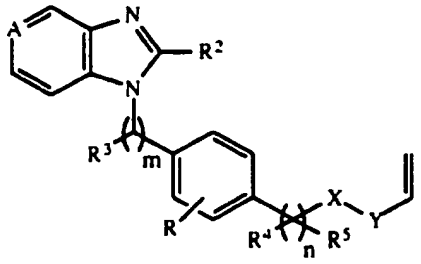
wherein R, R^2, R^3, R^4, R^5, R^9, Z, m, n, A are as defined in formula I. The amidation may be facilitated by using a carbodiimide condensing agent or an activated derivative of the acid (II) as for the esterification.

Route 3

Compounds of the invention in which Z represents an alkenyl group may be prepared by a palladium catalysed cross coupling reaction between a halide of formula (V) and an alkenyl compound of formula (VI):



(V)

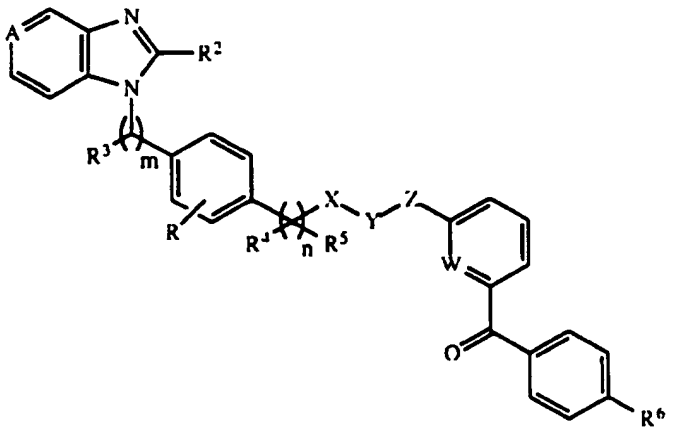


(VI)

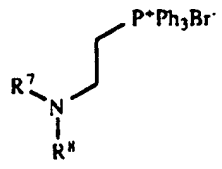
wherein R, R^2, R^3, R^4, R^5, R^6, R^7, R^8, W, X, Y, m, n, A, B and D are as defined in formula (I) and K represents a halide (preferably bromide). The reaction is typically performed in the presence of palladium acetate and a triaryl phosphine such as triphenyl phosphine. The reaction may be performed at room temperature or may require heating at up to 200°C in a sealed vessel.

Route 4

Compounds of the invention in which B and D taken together represent -C=C- may be prepared by the Wittig reaction between a ketone of formula (VII) and a phosphonium salt of formula (VIII).



(VII)

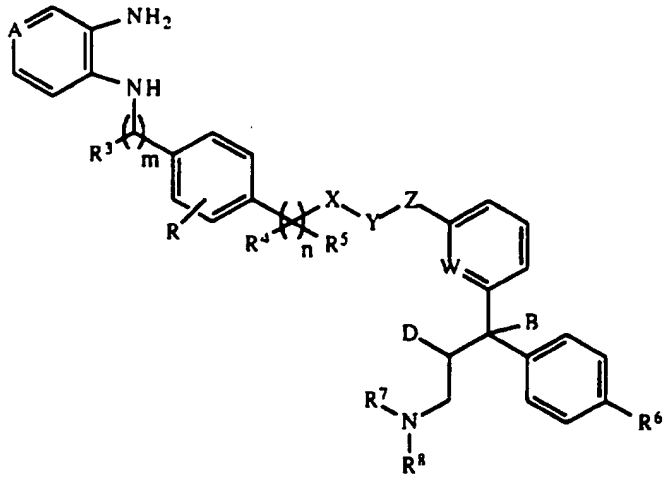


(VIII)

wherein R, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, W, X, Y, Z, m, n, and A are as defined in formula I. This reaction may be performed in the presence of a suitable base (eg. N-butyl lithium) in an appropriate solvent (eg. toluene)

Route 5

Compounds of formula (I) may also be prepared by a process comprising reaction of a diamino compound of formula (IX), with an acid of formula (X) or an activated derivative thereof.



(IX)

R^2COOH

(X)

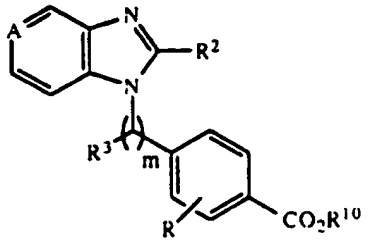
Wherein R, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, W, X, Y, Z, m, n, A, B and D are as defined in formula I. This reaction is analogous to that described previously in WO 92/03423 and suitable process conditions may be found therein.

The starting carboxylic acids of formula (II) for routes 1 and 2 may be prepared by routes previously described in the literature eg EP-085959-A2 (Wellcome).

Corresponding sulphonic acids, which may be used to prepare compounds of formula (I) where Y represents a sulphonyl group, may be prepared using similar chemistry. The sulphonic acid group may be introduced using the Wittig reaction (C. Gennari, B. Salom, D. Potenza, A. Williams; Angew Chem. Int. Ed. Engl., **33**

(20), 2067-2069, 1994). The sulphonic acids may be converted to sulphonyl chlorides, for example by treatment with triphenylphosphine and sulphuryl chloride and then coupled to amines of formula (IV).

Intermediates (III), (IV), (VI) and (VII) where n = 1, may be prepared *via* carboxylic acid ester derivatives of formula (XI)



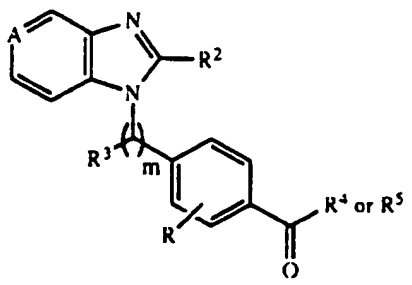
(XI)

wherein R, R^2, R^3, m, and A are as defined in formula (I) and R^{10} represents C_1-C_6 alkyl or benzyl,

Compounds of formula (XI) may be prepared using methods described in the literature eg WO-A-93/16075 (British Biotechnology), WO-A-90/11280 (Pfizer), WO-A-92/14734 (Pfizer).

Reduction of (XI) with for example lithium aluminium hydride or reaction with alkyl lithium (eg MeLi) or grignard reagents (eg MeMgBr) yields alcohols of formula (III).

When either R^4 or R^5 represents a hydrogen atom, alcohols of formula (III) may be oxidized with for example manganese dioxide to provide aldehydes or ketones of formula (XII)



(XII)

wherein R, R^2, R^3, R^4, R^5, m, and A are as defined in formula (I).

Aldehydes and ketones of formula (XII) may be reduced or treated with alkyl lithium and grignard reagents as above to provide a range of alcohols of formula (III). Alternatively compounds of formula (XII) may be subjected to a reductive amination reaction with an amine of formula R^9NH_2 either in the presence of a reducing agent such as sodium cyanoborohydride or using a palladium catalyst under an atmosphere of hydrogen gas to provide compounds of formula (IV).

When for alcohols of formula (III) R^4 and R^5 are equivalent (but not hydrogen) they may be prepared by the reaction of esters of formula (XI) with alkyl lithium or alkyl grignard reagents.

When for amines of formula (IV) R^4, R^5 and R^9 are hydrogen these compounds may be prepared by reaction of the mesylate of the alcohol (III) with sodium azide followed by reduction either by hydrogenation over a palladium catalyst or in the presence of triphenylphosphine.

Intermediates (IV), (VI) and (VII) wherein n = 0, X is NR9; and R, R^2, R^3, R^4, R^5, R^9, Y, m and A are as defined in formula (I) may be prepared using conventional methods described in the literature eg WO-A-93/16075 (British Biotechnology),

WO-A-90/11280 (Pfizer), WO-A-92/14734 (Pfizer).

As mentioned above, the invention makes available a class of compounds having a desirable balance of H_1 and PAF antagonist activity.

Accordingly in another aspect, this invention concerns:

(i) a method of management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by histamine and/or PAF in mammals, in particular in humans, which method comprises administering to the mammal an effective amount of a compound as defined with respect to formula (I) above, or a pharmaceutically acceptable salt thereof; and

(ii) a compound as defined with respect to formula (I) for use in human or veterinary medicine, particularly in the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by histamine and/or PAF; and

(iii) the use of a compound as defined with respect to formula (I) in the preparation of an agent for the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by histamine and/or PAF.

Diseases or conditions mediated by histamine and/or PAF, but which probably include contributions from both agents, include hypotension, thrombocytopenia, bronchoconstriction, circulatory shock, increased vascular permeability (oedema/erythema), allergic rhinitis, sinusitis, asthma, dermatitis, psoriasis, urticaria, anaphylactic shock, conjunctivitis, pruritis, inflammatory bowel disease and colitis.

According to a further aspect of the invention there is provided a pharmaceutical or veterinary formulation comprising a compound of general formula (I) and a pharmaceutically and/or veterinarily acceptable carrier. One or more compounds of general formula (I) may be present in association with one or more non-toxic

pharmaceutically and/or veterinarily acceptable carriers and/or diluents and/or adjuvants and if desired other active ingredients. The pharmaceutical compositions containing compounds of general formula (I) may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs.

Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are

suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occuring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavouring and colouring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or

arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavouring and colouring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical application to the skin compounds of the invention may be made up into a cream, ointment, jelly, solution or suspension etc. Cream or ointment

formulations that may be used for the drug are conventional formulations well known in the art, for example, as described in standard text books of pharmaceutics such as the British Pharmacopoeia.

For topical applications to the eye, compounds of the invention may be made up into a solution or suspension in a suitable sterile aqueous or non-aqueous vehicle. Additives, for instance buffers, preservatives including bactericidal and fungicidal agents, such as phenyl mercuric acetate or nitrate, benzalkonium chloride or chlorohexidine, and thickening agents such as hypromellose may also be included.

Compounds of the invention may be administered parenterally in a sterile medium. The drug depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle.

Compounds of the invention may be used for the treatment of the respiratory tract by nasal or buccal administration of, for example, aerosols or sprays which can disperse the pharmacologic al active ingredient in the form of a powder or in the form of drops of a solution or suspension. Pharmaceutical compositions with powder-dispersing properties usually contain, in addition to the active ingredient, a liquid propellant with a boiling point below room temperature and, if desired, adjuncts, such as liquid or solid non-ionic or anionic surfactants and/or diluents. Pharmaceutical compositions in which the pharmacological active ingredient is in solution contain, in addition to this, a suitable propellant, and furthermore, if necessary, an additional solvent and/or a stabiliser. Instead of the propellant, compressed air can also be used, it being possible for this to be produced as required by means of a suitable compression and expansion device.

Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). For example, inflammation may be

effectively treated by the administration of from about 0.01 to 50 mg of the compound per kilogram of body weight per day (about 1.0 mg to about 3.5 g per patient per day). The dosage employed for the topical administration will, of course, depend on the size of the area being treated. For the eyes each dose will be typically in the range from 10 to 100 mg of the drug.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for the oral administration of humans may contain from 0.5 mg to 5 g of active agent compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy.

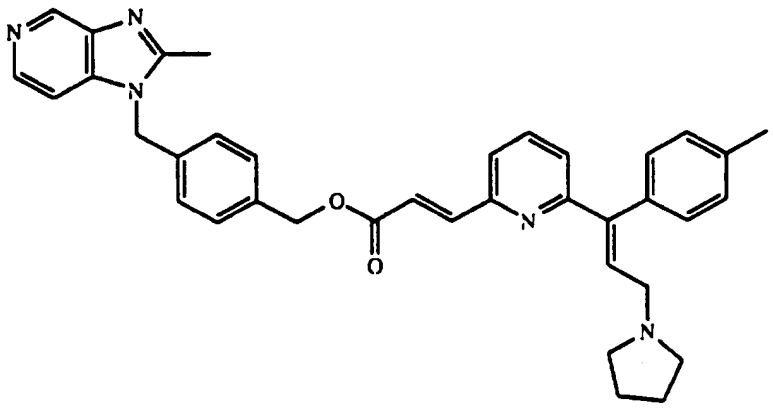
The following examples illustrate the invention, but are not intended to limit the scope in any way. The following abbreviations have been used in the examples:-

DCM - Dichloromethane
MPLC - Medium Pressure Liquid Chromatography
DMF - Dimethylformamide

Column chromatography was performed with flash grade silica gel. ^{1}H-NMR and ^{13}C-NMR were recorded on a Bruker AMX-500 spectrometer at 500MHz and 125.72 MHz respectively. $CDCl_3$ or d_4-methanol were used as a solvent and internal reference and spectra are reported as δ ppm from TMS.

Example 1

3-[6-(3-Pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylic acid 4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl ester.



(a) 4-(1H-2-Methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl alcohol.

4-(1H-2-Methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl methyl ester (500mg, 1.78mmol) was stirred in anhydrous THF (15mL) at 0°C and treated under argon with lithium aluminium hydride (68mg, 1.78mmol). After stirring at 0°C for 3 hours, water (0.75mL) and 15% w/v aqueous sodium hydroxide (0.25mL) were added. Following the formation of a gelatinous precipitate the mixture was filtered through Kieselguhr and washed with THF (2 x 15mL). The solvent was evaporated under reduced pressure and the resulting solid purified by column chromatography on silica gel, eluting with 8-10% methanol/DCM, to provide 4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl alcohol as an off white solid (353mg,78%).

^{1}H-NMR; δ ($CDCl_3$), 8.94 (1H, s), 8.28 (1H, d, J=5.6Hz), 7.34 (2H, d,

J=8.1Hz), 7.15 (1H, d, J=4.9Hz), 7.01 (2H, d, J=8.1Hz), 5.31 (2H, s), 4.69 (2H, s) and 2.47 (3H, s).

^{13}C-NMR; δ ($CDCl_3$), 153.7, 141.8, 141.7, 141.6, 140.4, 139.6, 133.8, 127.7, 126.4, 105.0, 64.3, 47.2 and 14.0.

(b) 3-[6-(3-Pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylic acid 4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl ester.

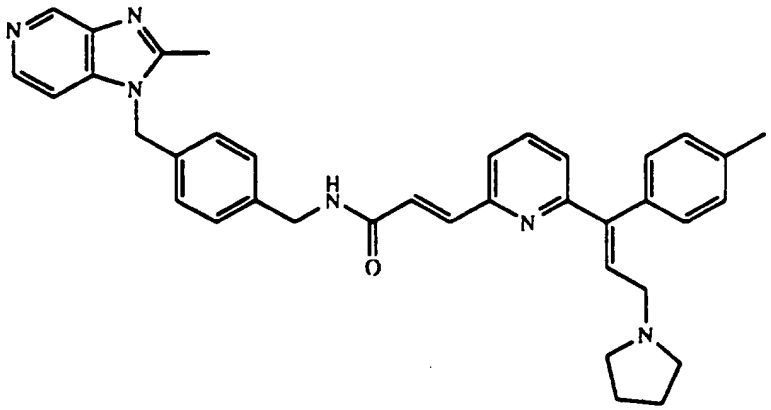
3-[6-(3-Pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylic acid (188mg, 0.54mmol) was dissolved in anhydrous DCM (10mL) and treated under argon with 4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl alcohol (150mg, 0.59mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (125mg, 0.65mmol) and 4-dimethylaminopyridine (cat.). After stirring at room temperature for 72 hours the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel, eluting with 5-10% methanol/DCM, to provide the title compound as a purple glass (212mg, 67%).

^{1}H-NMR; δ ($CDCl_3$), 9.01 (1H, s), 8.36 (1H, d, J=5.5Hz), 7.69 (1H, d, J=15.8Hz), 7.53 (1H, t, J=7.7Hz), 7.40 (2H, d, J=8.1Hz), 7.27-7.16 (5H, m), 7.08-7.05 (4H, m), 7.01 (1H, d, J=15.7Hz), 6.88 (1H, d, J=7.8Hz), 5.34 (2H, s), 5.23 (2H, s), 3.49 (2H, d, J=7.2Hz), 2.91 (4H, bs), 2.60 (3H, s), 2.39 (3H, s), and 1.94 (4H, bs).

^{13}C-NMR; δ ($CDCl_3$), 166.5, 157.1, 153.6, 151.9, 144.1, 142.0, 141.9, 140.4, 139.8, 137.8, 137.2, 136.3, 134.9, 134.0, 129.5, 129.4, 129.0, 126.5, 123.3, 123.1, 122.2, 122.0, 104.9, 65.7, 53.6, 53.3, 47.1, 23.5 and 14.1.

Example 2

N-[4-(1H-2-Methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]-3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylamide.



(a) 4-(1H-2-Methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl bromide dihydrobromide.

4-(1H-2-Methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl alcohol (850mg, 3.36mmol) was dissolved in hydrobromic acid (48% in water, 25mL) and heated under reflux (100°C) for 24 hours. The solvent was evaporated under reduced pressure and the residue azeotroped with diethylether to provide 4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl bromide as the dihydrobromide salt (1.59g, quantitative).

^{1}H-NMR; δ (d_4-methanol), 9.28 (1H, s), 8.59 (1H, d, J=7.2Hz), 8.19 (1H, d, J=6.3Hz), 7.45 (2H, d, J=8.2Hz), 7.24 (2H, d, J=8.2Hz), 5.75 (2H, s), 4.55 (2H, s) and 2.78 (3H, s).

(b) 4-(1H-2-Methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl azide dihydrobromide.

4-(1H-2-Methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl bromide dihydrobromide (755mg, 1.58mmol) and sodium azide (308mg, 4.74mmol) were dissolved in anhydrous DMF (10mL) and stirred under an argon atmosphere for 24 hours. The solvent was evaporated under reduced pressure to provide 4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl azide dihydrobromide as an orange paste (700mg, quantitative).

^{1}H-NMR; δ (d_4-methanol), 8.82 (1H, s), 8.30 (1H, d, J=5.7Hz), 7.59 (1H, d, J=5.6Hz), 7.35 (2H, d, J=8.0Hz), 7.20 (2H, d, J=8.0Hz), 5.60 (2H, s), 4.35 (2H, s) and 2.65 (3H, s).

(c) 4-(1H-2-Methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl amine dihydrobromide.

4-(1H-2-Methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl azide dihydrobromide (700mg, 1.58 mmol) was dissolved in methanol (25mL) and treated with palladium on charcoal (50mg) as a suspension in methanol (5mL). Hydrogen gas was bubbled through the mixture for 4.5 hours. It was then filtered and solvent evaporated under reduced pressure to give 4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl amine dihydrobromide as a pale yellow foam (792mg, quantitative).

^{1}H-NMR; δ (d_4-methanol), 8.82 (1H, s), 8.29 (1H, d, J=5.6Hz), 7.55 (1H, d, J=5.7Hz), 7.35 (2H, d, J=8.0Hz), 7.15 (2H, d, J=8.1Hz), 5.54 (2H, s), 3.80 (2H, s) and 2.64 (3H, s).

(d) N-[4-(1H-2-Methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]-3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylamide.

4-(1H-2-Methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl amine dihydrobromide (780mg, 1.88mmol) was dissolved in anhydrous DMF (20mL) and treated under argon with 3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylic acid (596mg, 1.71mmol), 1-hydroxybenzotriazole (300mg, 2.22mmol), N-(3-

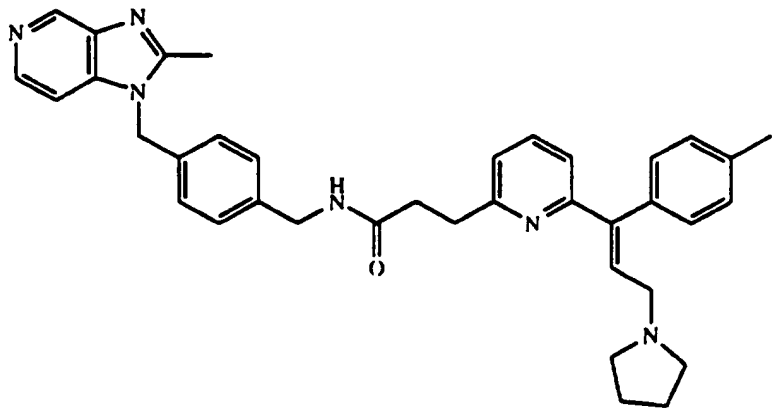
dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (393mg, 2.05mmol) and 4-methylmorpholine (519mg, 5.13mmol).The reaction mixture was stirred at room temperature for 96 hours, after which the solvent was evaporated under reduced pressure. The residue was dissolved in DCM (60mL) and washed with saturated sodium bicarbonate (40mL) and brine (40mL). After drying over anhydrous sodium sulphate, the organic phase was evaporated under reduced pressure to yield a red oil. Purification by column chromatography on silica gel, eluting with 5-10% methanol/DCM, provided N-[4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]-3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylamide as a pink foam (374mg, 38%).

^{1}H-NMR; δ ($CDCl_3$), 9.00 (1H, s), 8.35 (1H, d, J=5.5Hz), 7.73 (1H, d, J=15.0Hz), 7.64 (1H, t, J=7.1Hz), 7.58 (1H, d, J=14.9Hz), 7.50 (1H, t, J=7.8Hz), 7.36 (2H, d, J=8.1Hz), 7.25 (3H, m), 7.16 (2H, m), 7.05 (2H, d, J=7.9Hz), 6.99 (2H, d, J=8.1Hz), 6.75 (1H, d, J=7.9Hz), 5.29 (2H, s), 4.59 (2H, d, J=6.0Hz), 3.53 (2H, d, J=7.2Hz), 2.94 (4H, bs), 2.59 (3H, s), 2.42 (3H, s), and 1.92 (4H, m).

^{13}C-NMR; δ ($CDCl_3$), 166.1, 155.7, 152.3, 144.1, 141.9, 141.8, 140.4, 139.1, 138.1, 138.0, 137.3, 133.6, 129.6, 129.4, 128.6, 126.7, 126.4, 123.4, 122.2, 105.0, 54.6, 53.8, 47.2, 43.0, 23.3, 21.3 and 14.1.

Example 3

N-[4-(1H-2-Methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]-3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-propionylamide.



(a) Methyl-(E)-3-(6-[3-pyrrolidin-1-yl-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-acrylate.

A solution of (E)-3-(6-[3-pyrrolidin-1-yl-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-acrylic acid (2.04g, 5.9mmol) in methanol (50mL) was treated with concentrated hydrochloric acid (10mL) and stirred at room temperature for 6 days. The reaction was neutralised with sodium hydrogen carbonate and solvent removed under reduced pressure. DCM was added to the filtrate and inorganic solids removed by filtration. Concentration of the filtrate under reduced pressure yielded methyl-(E)-3-(6-[3-pyrrolidin-1-yl-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-acrylate as a pink foam (1.98g, 93%).

^{1}H-NMR; δ ($CDCl_3$), 7.70 (1H, d, J=15.7Hz), 7.57 (1H, t, J=7.7Hz), 7.30 (1H, t, J=7.6Hz), 7.25 (2H, d, J=8.3Hz), 7.17 (1H, d, J=7.2Hz), 7.10 (2H, dt, J=8.2, 1.8Hz), 6.96 (1H, d, J=15.6Hz), 6.93 (1H, d, J=7.9Hz), 3.83 (3H, s), 3.65 (2H, brs), 2.85 (4H, brm), 2.41 (3H, s), 2.04 (4H, brm).

(b) Methyl-3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-propionate.

A degassed solution of sodium borohydride (629mg, 16.6mmol) and tellurium (898mg, 7.04mmol) in ethanol (30mL) was heated at 80°C, under an inert atmosphere for 1 hour. The resulting purple/brown suspension was cooled to room temperature. Finely ground, degassed, ammonium chloride (1.48g, 27.6mM) was added followed by a solution of methyl-(E)-3-(6-[3-pyrrolidin-1-yl-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-acrylate (1.00g, 2.76mmol) in ethanol (10mL). The reaction was allowed to stir at room temperature for 18 hours under an inert atmosphere and then for a further 2 hours open to the atmosphere. The reaction mixture was filtered through a pad of kieselguhr and the filtrate concentrated under reduced pressure. The resulting solid was triturated with DCM (3x20mL) and the combined washings filtered and concentrated under reduced pressure to yield methyl-3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-propionate as a pale pink foam (1.084g, 108%). The product was contaminated with approximately 25% ethyl ester and was used crude in the following reaction.

^{1}H-NMR; δ ($CDCl_3$), 7.38 (1H, t, J=7.9Hz), 7.20 (2H, d, J=7.9Hz), 7.13 (1H, m), 7.06 (2H, d, J=7.9Hz), 7.00 (1H, d, J=7.6Hz), 6.66 (1H, d, J=8.0Hz), 3.68 (3H, s), 3.27 (2H, d, J=8.3Hz), 3.11 (2H, m), 2.86 (2H, m), 2.65 (4H, m), 2.38 (3H, s) and 1.82 (4H, m).

(c) Sodium, 3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-propionate.

A solution of methyl-3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-propionate (261mg, 0.7mmol) in a mixture of THF and water (7mL, 3:1) was treated with a solution of sodium hydroxide (0.733mmol, in 1.5mL water) and stirred at 60°C for 24 hours. The solvent was removed under reduced pressure to yield sodium, 3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-propionate (286mg, quantitative).

^{1}H-NMR; δ (d_4-methanol), 7.48 (1H, t, J=7.7Hz), 7.27 (2H, d, J=7.8Hz),

7.14 (1H, d, J=7.6Hz), 7.05 (2H, d, J=7.9Hz), 6.95 (1H, t, J=6.9Hz), 6.70 (1H, d, J=7.8Hz), 3.24 (2H, d, J=7.0Hz), 3.09 (2H, t, J=7.7Hz), 2.60 (6H, m), 2.37 (3H, s) and 1.80 (4H, m).

^{13}C-NMR; δ (d_4-methanol), 180.3, 161.3, 157.3, 142.8, 137.1, 136.6, 135.2, 129.4, 129.3, 129.3, 129.3, 128.9, 128.8, 128.7, 128.7, 127.6, 121.0, 119.6, 54.0, 53.4, 37.5, 34.6, 28.5, 22.9, 22.8, 22.7 and 19.9.

(d) N-[4-(1H-2-Methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]-3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-propionylamide.

A solution of 4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzylamine (240mg, 0.952mmol), sodium, 3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-propionate (286mg, 768mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (221mg, 1.15mmol) and hydroxybenzotriazole (124mg, 0.95mmol) in DMF (8mL) was stirred under an inert atmosphere at room temperature for 18 hours. DMF was removed under reduced pressure and the residue partitioned between DCM and saturated sodium bicarbonate solution. The organic layer was separated, washed with brine, dried over magnesium sulphate, filtered and concentrated. The product was purified by column chromatography eluting with 2-10% methanol/DCM. Product containing fractions were combined and solvent removed to yield N-[4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]-3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-propionylamide (284mg, 63%) as a yellow foam.

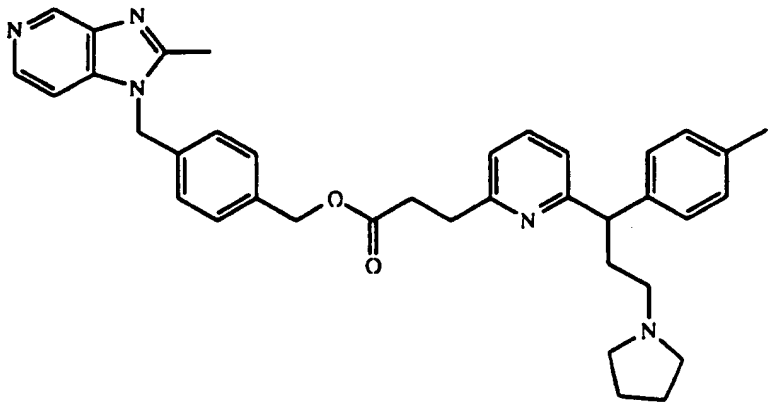
^{1}H-NMR; δ ($CDCl_3$), 8.93 (1H, s), 8.25 (1H, d, J=5.6Hz), 7.32 (1H, t, J=7.8Hz), 7.27 (1H, m), 7.09 (2H, d, J=7.8Hz), 7.07 (1H, d, J=5.7Hz), 7.01 (2H, d, J=8.1Hz), 6.91 (4H, m), 6.84(2H, d, J=8.1Hz), 6.69 (1H, d, J=7.8Hz), 5.20 (2H, s), 4.24 (2H, d, J=6.0Hz), 3.05 (2H, t, J=6.9Hz), 3.03 (2H, d, J=7.0Hz), 2.70 (2H, t, J=7.0Hz), 2.50 (3H, s), 2.37 (4H, m), 2.30

(3H, s), and 1.63 (4H, m).

^{13}C-NMR; δ ($CDCl_3$), 173.1, 159.2, 157.3, 153.5, 141.8, 141.7, 141.6, 140.3, 139.8, 139.3, 136.9, 136.7, 135.3, 133.5, 130.2, 129.6, 129.0, 128.0, 128.0, 128.0, 126.3, 121.5, 119.7, 104.9, 54.7, 54.1, 47.0, 42.6, and 14.0.

Example 4

N-[4-(1H-2-Methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]-3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-propyl)-pyridin-2-yl]-propionate.



(a) Sodium, 3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-propyl)-pyridin-2-yl]-propionate

A solution of methyl-(E)-3-(6-[3-pyrrolidin-1-yl-{4-tolyl}-prop-1E-enyl]-pyridin-2-yl)-acrylate (Example 3, step a, 302mg, 0.83mmol) in ethanol (20mL) was treated with palladium catalyst (100mg, 10%Pd on charcoal) under an inert atmosphere. Hydrogen gas was bubbled through the reaction mixture which was then stirred

under an atmosphere of hydrogen for 18 hours. The catalyst was removed by filtration and the filtrate concentrated under reduced pressure to yield a brown oil. The residue was dissolved in a mixture of THF and water (5mL, 4:1) and treated with a solution of sodium hydroxide (0.84mmol, 1.7mL water). The reaction mixture was heated at 45°C for 18 hours. Solvent was removed under reduced pressure to yield sodium, 3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-propyl)-pyridin-2-yl]-propionate as a pale brown gum (306mg, 99%).

^{1}H-NMR; δ (d_4-methanol), 7.56 (1H, d, J=7.7Hz), 7.20 (2H, d, J=8.1Hz), 7.07 (4H, m), 4.00 (1H, m), 3.05 (2H, t, J=7.9Hz), 2.55 (2H, t, J=8.4Hz), 2.48 (4H, m), 2.35 (3H, m), 2.24 (3H, s), 2.24 (1H, m) and 1.75 (4H, m).

^{13}C-NMR; δ (d_4-methanol),180.4, 163.0, 161.1, 140.1, 137.2, 135.7, 128.7, 127.5, 120.2, 119.4, 54.7, 53.6, 51.1, 37.7, 34.4, 33.6, 22.7 and 19.7.

(b) N-[4-(1H-2-Methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]-3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-propyl)-pyridin-2-yl]-propionate.

A solution of sodium, 3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-propyl)-pyridin-2-yl]-propionate (306mg, 0.83mmol), 4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl alcohol (252mg, 1.00mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (255mg, 1.33mmol) and dimethylaminopyridine (20mg, catalytic) in DCM (10ml) was stirred at room temperature for 240 hours. The reaction mixture was partitioned between DCM and saturated sodium bicarbonate solution. The organic layer was separated, washed with brine, dried over magnesium sulphate, filtered and concentrated to a brown gum. The product was purified by column chromatography on silica gel eluting with 20 % methanol/DCM. Product containing fractions were combined and solvent removed to yield N-[4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]-3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-propyl)-pyridin-2-yl]-propionate as a colourless glass

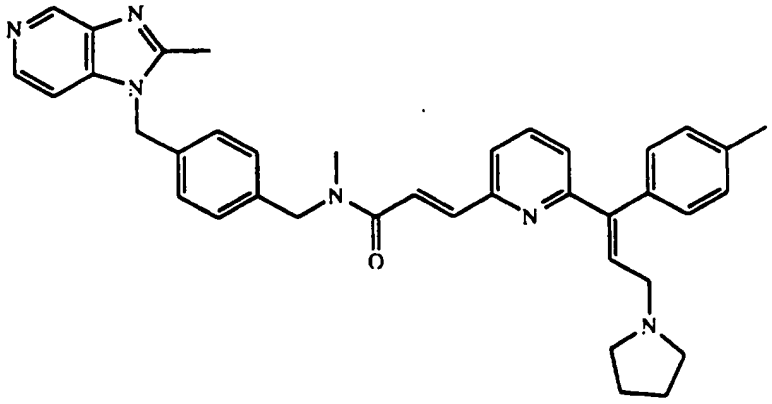
(17mg, 3%).

^{1}H-NMR; δ ($CDCl_3$), 9.02 (1H, s), 8.35 (1H, d, J=5.6Hz), 7.39 (1H, t, J=7.8Hz), 7.22 (2H, d, J=8.1Hz), 7.19 (1H, dd, J=5.6Hz), 7.15 (2H, d, J=8.0Hz), 7.05 (2H, d, J=8.0Hz), 6.98 (2H, d, J=8.1Hz), 6.93 (1H, d, J=7.6Hz), 6.89 (1H, d, J=7.7Hz), 5.34 (2H, s), 5.07 (2H, m), 3.99 (1H, t, J=7.6Hz), 3.12 (2H, t, J=7.2Hz), 2.95 (4H, brm), 2.86 (2H, dt, J=7.0 and 2.4Hz), 2.72 (2H, m), 2.59 (1H, m), 2.59 (3H, s), 2.39 (1H, m), 2.26 (3H, s) and 1.93 (4H, m).

^{13}C-NMR; δ ($CDCl_3$), 172.9, 161.5, 158.8, 153.6, 142.0, 141.9, 140.4, 139.8, 139.6, 136.8, 136.4, 135.0, 129.3, 128.7, 127.7, 127.7, 126.4, 120.8, 120.7, 104.9, 65.5, 54.4, 53.8, 53.7, 50.5, 47.1, 33.0 and 14.1.

Example 5

N-Methyl-N-[4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]-3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylamide.



(a) 4-(1H-2-Methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzaldehyde.

Manganese (IV) dioxide (6.3g, 72mmol) was added to a solution of 4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl alcohol (Example 1, step a, 1.90g, 7.51mmol) in DCM (30mL). The reaction was stirred at room temperature for 24

hours. The reaction mixture was filtered through kieselguhr and concentrated to a colourless oil. The product was purified by column chromatography on silica gel eluting with 5% methanol/DCM. Product containing fractions were combined and solvent removed under reduced pressure to yield 4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzaldehyde as a white solid (1.50g, 80%).

^{1}H-NMR; δ ($CDCl_3$), 9.91 and 9.91 (1H, 2 x s), 8.97 (1H, s), 8.30 (1H. m), 7.78 (2H, d, J=8.2Hz), 7.13 (2H, d, J=8.0Hz), 7.10 (1H, m), 5.36 (2H, s), 2.53 (3H, s).

(b) N-Methyl-N-[4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]amine.

Palladium catalyst (150mg, 10% on charcoal) was added to a solution of 4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzaldehyde (1.50g, 5.98mmol) in ethanol (20mL) under an inert atmosphere. A solution of methylamine in ethanol (1mL, excess of a 33% solution) was added and the reaction stirred under an atmosphere of hydrogen gas for 18 hours. The catalyst was removed by filtration and the filtrate concentrated under reduced pressure to leave a colourless oil. The product was purified by column chromatography on silica gel eluting with 50% methanol/DCM. Product containing fractions were combined and solvent removed to yield N-methyl-N-[4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]amine as a white solid (1.05g, 70%).

^{1}H-NMR; δ ($CDCl_3$), 8.99 (1H, d, J=4.1Hz), 8.35-8.32 (1H, m), 7.27 (2H, d, J=6.3Hz), 7.17-7.15 (1H, m), 7.00 (2H, d, J=7.5Hz), 5.30 (2H, s), 3.71 (2H, s), 2.58 (3H, s), 2.41 (3H, s).

^{13}C-NMR; δ ($CDCl_3$), 153.6, 141.9, 140.4, 139.8, 129.0, 126.4, 104.9, 55.4, 47.2, 36.0 and 14.1.

(c) N-Methyl-N-[4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]-3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylamide.

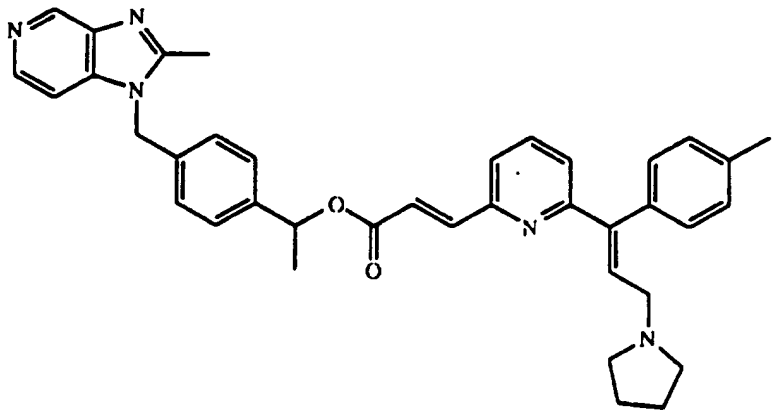
A solution of 3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylic acid (940mg, 2.71mmol), N-m ethyl-N-[4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]amine (600mg, 2.25mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (520mg, 2.71mmol) and hydroxybenzotriazole (365mg, 2.71mmol) in DMF (20mL) was allowed to stand at room temperature for 48 hours. The reaction mixture was poured into water (100mL) and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate and brine before drying over magnesium sulphate, filtration and removal of solvent to yield a pink oil. The product was purified by column chromatography on silica gel eluting with 25% methanol/DCM. Product containing fractions were combined and solvent removed under reduced pressure to leave N-methyl-N-[4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]-3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylamide as a pale pink solid (115mg, 9%).

^{1}H-NMR; δ ($CDCl_3$), 9.01 and 9.00 (1H, 2 x s), 8.36 and 8.33 (1H, 2 x d, J=5.5Hz), 7.72-7.66 (2H, m), 7.53-7.48 (1H, m), 7.32-7.22 (7H, m), 7.20-7.00 (4H, m), 6.86-6.84 (1H, m), 5.31 (2H, s), 4.78 and 4.68 (2H, 2 x s), 3.47 and 3.38 (2H, 2 x bs), 3.18 and 3.01 (3H, 2 x s), 2.95-2.64 (4H, m), 2.60 and 2.59 (3H, 2 x s), 2.40 and 2.35 (3H, 2 x s), and 1.90 and 1.77 (4H, 2 x m).

^{13}C-NMR; δ ($CDCl_3$), 166.9, 166.6, 153.6, 153.5, 152.5, 152.4, 142.0, 141.8, 141.4, 141.2, 140.4, 140.3, 139.8, 137.6, 137.2, 134.3, 134.0, 129.4, 129.3, 128.8, 127.8, 126.8, 126.5, 123.6, 123.4, 122.6, 122.5, 121.7, 121.4, 104.9, 54.2, 54.1, 53.6, 53.5 and 14.1.

Example 6

3-[6-(3-Pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylic acid 1-[4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-phenyl]-ethylester.



(a) 1-[4-(1H-2-Methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-phenyl]-ethanol.

A solution of 4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzaldehyde (Example 5, step (a), 1.10g, 4.40mmol) in THF (25mL) was stirred and treated dropwise with a solution of methylmagnessium bromide (1.6mL of 3.0M solution in THF, 4.8mmol). The reaction was stirred at room temperature for 2 hours before the addition of more grignard reagent (1.0mL). After 1 hour the reaction was quenched with water (1mL) and partitioned between water and DCM. The organic layer was separated, dried over magnesium sulphate, filtered and concentrated to leave a yellow oil. The product was purified by column chromatography on silica gel, eluting with 10%methanol/DCM. Product containing fractions were combined and solvent removed under reduced pressure to yield 1-[4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-phenyl]-ethanol as a white solid (205mg, 17.5%).

^{1}H-NMR; δ ($CDCl_3$), 8.81 (1H, s), 8.15 (1H, d, J=5.5Hz), 7.33 (2H, d, J=8.1Hz), 7.09-7.08 (1H, m), 6.95 (2H, d, J=8.1Hz), 5.26 (2H, s), 4.89-4.86 (1H, q, J=6.4Hz), 2.51 (3H, s), 1.44 (3H, d, J=6.4Hz).

(b) 3-[6-(3-Pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylic acid 1-[4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-phenyl]-ethylester.

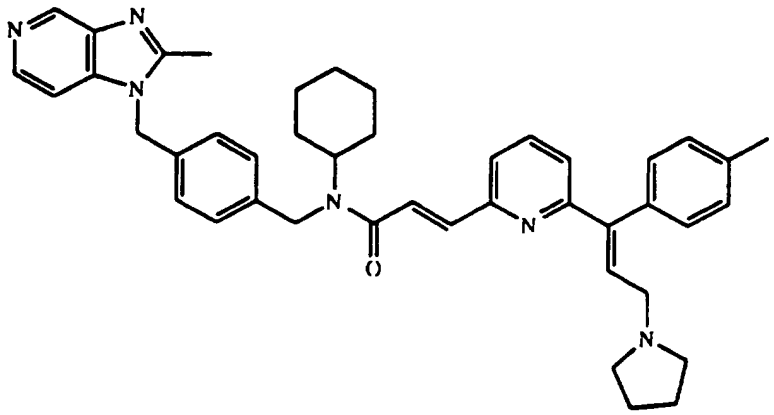
A solution of 3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylic acid (298mg, 0.85mmol), 1-[4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-phenyl]-ethanol (190mg, 0.71mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (164mg, 0.85mmol) and dimethylaminopyridine (20mg, calalytic) in DMF (10mL) was allowed to stand at room temperature for 96 hours. DMF was removed under reduced pressure and the product partitioned between DCM and water. The organic layer was separated, washed with brine, dried over magnesium sulphate, filtered and concentrated to leave a pink oil. The product was purified by column chromatography eluting with 8% methanol/DCM. Product containing fractions were combined and concentrated under reduced pressure to leave 3-[6-(3-Pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylic acid 1-[4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-phenyl]-ethylester as a white foam (50mg, 12%).

^{1}H-NMR; δ ($CDCl_3$), 8.99 (1H, s), 8.34 (1H, d, J=5.6Hz), 7.64 (1H, d, J=15.7Hz), 7.51 (1H, t, J=7.8Hz), 7.38 (2H, d, J=8.2Hz), 7.22 (2H, d, J=7.8Hz), 7.22-7.17 (3H, m), 7.07-6.99 (5H, m), 6.85 (1H, d, J=7.8Hz), 5.87 (1H, q, J=6.5Hz), 5.30 (2H, s), 3.42 (2H, d, J=6.9Hz), 2.82 (4H, brs), 2.58 (3H, s), 2.28 (3H, s), 1.89 (4H, bs), and 1.58 (3H, d, J=6.5Hz).

^{13}C-NMR; δ ($CDCl_3$), 166.0, 157.3, 153.6, 151.9, 143.8, 142.0, 141.8, 140.4, 139.8, 137.7, 137.1, 134.5, 134.2, 129.4, 126.9, 126.5, 123.2, 123.1, 122.9, 122.4, 104.9, 72.0, 53.9, 53.5, 47.0, 23.5, 22.3, 21.2, and 14.1.

Example 7

N-Cyclohexyl-N-[4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]-3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylamide.



(a) N-Cyclohexyl-N-[4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]amine.

A solution of 4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzylamine (518mg, 2.05mmol) and cyclohexanone (222mg, 2.26mmol) in toluene (10ml) was heated under reflux and the distillate collected in a Dean and Stark trap. After 2.5 hours the solvent was removed under reduced pressure to a bright yellow paste. The residue was dissolved in anhydrous methanol, cooled to 0°C and treated with sodium borohydride (74mg, 1.96mmol). The reaction was stirred at 0°C for 2 hours. Solvent was removed under reduced pressure and the residue partitioned between DCM and saturated aqueous sodium bicarbonate solution. The organic phase was separated, dried over sodium sulphate, filtered and evaporated to provide N-cyclohexyl-N-[4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-

benzyl]amine, as a yellow foam (573mg, 83%).

^{1}H-NMR; δ ($CDCl_3$), 9.01 (1H, s), 8.36 (1H, d, J=5.5Hz), 7.32-7.26 (2H, m), 7.18-7.16 (1H, m), 6.99 (2H, d, J=8.1Hz), 5.30 and 5.29 (2H, 2xs), 3.78 (2H, s), 2.59 (3H, s), 2.46-2.42 (1H, m), 1.90-1.87 (2H, m), 1.74-1.70 (2H, m), 1.61-1.58 (2H, m) and 1.27-1.05 (4H, m).

(b) N-Cyclohexyl-N-[4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]-3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylamide.

A solution of 3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylic acid (540mg, 1.55mmol), N-cyclohexyl-N-[4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]amine (573mg, 1.71mmol), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (447mg, 2.33mmol) and hydroxybenzotriazole (20mg) in DMF (15mL) was allowed to stand at room temperature for 120 hours. DMF was removed under reduced pressure and the residue partitioned between DCM and saturated aqueous sodium bicarbonate solution. The organic layer was separated and washed with brine before drying over magnesium sulphate, filtration and removal of solvent to yield a pink oil. The product was purified by column chromatography on silica gel eluting with 10% methanol/DCM. Product containing fractions were combined and solvent removed under reduced pressure to leave N-cyclohexyl-N-[4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]-3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylamide as a pale pink glass (105mg, 10%).

^{1}H-NMR; δ ($CDCl_3$), 9.01 (1H, s), 8.36 (0.62H, d, J=5.5Hz), 8.29 (0.38H, d, J=5.6Hz), 7.67 (1H, m), 7.56-7.42 (1H, m), 7.32-6.81 (13H, bm), 5.30 (2H, s), 4.65 (2H, s), 3.97 (1H, m), 3.23 (1.17H, d, J=6.7Hz), 3.09 (0.83H, d, J=6.8Hz), 2.59 (3H, s), 2.55 (3H, s), 2.38 (4H, m), 1.76-1.62 (9H, bm) and 1.46-1.09 (5H, bm).

^{13}C-NMR; δ ($CDCl_3$), 167.1, 166.8, 161.4, 158.2, 157.8, 153.6, 152.4, 152.3, 141.9, 141.6, 141.3, 140.4, 139.9, 139.8, 137.0, 136.9, 136.8, 135.3, 133.8, 131.0, 130.7, 129.7, 129.7, 129.0, 127.7, 127.2, 126.8, 126.3, 123.0, 122.6, 122.4, 122.3, 122.2, 121.6, 105.0, 104.8, 77.4, 57.8, 54.7, 54.2, 54.1, 54.0, 47.2, 47.1, 46.6, 44.9, 32.3, 30.8, 29.7, 25.7, 25.5, 25.3, 23.5, 21.2 and 14.1.

Pharmacology Example 1

Histamine Induced Bronchoconstriction in the Anaesthetised Guinea Pig

Following oral administration of test compound or vehicle by oral gavage, male Dunkin-Hartley guinea pigs (350-400g) were anaesthetised by intraperitoneal injection of 60mg.kg^{-1} sodium pentobarbitone (Sagatal, May & Baker UK). Through a midline incision of the neck, the trachea was cannulated and connected to a small animal respirator (Harvard, UK). Animals were artificially ventilated at a rate of 30 breaths per minute with a tidal volume of 8-10ml to give a resting tracheal inflation pressure of 15mmHg as measured by a physiological pressure transducer (type P23XL, Spectramed USA) connected to a side arm of the respiratory circuit.

The left jugular vein was cannulated for the administration of propranolol and for the infusion of histamine. A carotid artery was cannulated for the measurement of arterial blood pressure via a physiological pressure transducer (type P23XL, Spectramed USA). Blood pressure and tracheal inflation pressure were recorded on a thermal array chart recorder (type TA4000, Gould Electronics UK).

Following a suitable equilibration period, propranolol (1mg.kg^{-1} i.v. & 3mg.kg^{-1} s.c. Sigma Chemical Co. UK) was administered to inhibit any resulting catecholamine release following histamine administration.

Histamine infusion (10μg.kg^{-1}.min^{-1} at a rate of 10ml.hr^{-1} using a perfusion pump type Perfuser securer FT, B. Braun Germany) was started at the one hour time point following oral administration of the test compound or vehicle. Changes in tracheal inflation pressure and blood pressure of drug treated animals were compared with changes from vehicle treated animals and ED_{50} values determined. One dose of test compound was investigated per animal.

Results

Example	ED_{50} mg/kg *po*
1	0.5

Pharmacology Example 2

PAF Induced Bronchoconstriction in the Anaesthetised Guinea Pig

Following oral administration of test compound or vehicle, male Dunkin-Hartley guinea pigs (350-400g) were anaesthetised by intraperitoneal injection of 60mg.kg^{-1} sodium pentobarbitone (Sagatal, May & Baker UK). Through a midline incision of the neck, the trachea was cannulated with a length (3cm) of nylon tubing which was connected to a small animal respirator (Harvard, UK). Animals were artificially ventilated at a rate of 30 breaths per minute with a tidal volume of 8-10ml to give a resting tracheal inflation pressure of 15mmHg as measured by a physiological pressure transducer (type P23XL, Spectramed USA) connected to a side arm of the respiratory circuit.

A jugular vein was cannulated with an intraveinous catheter (type 3F with blue luer fitting, Portex UK) for the administration of a bolus dose of propranolol and for the later administration of bolus PAF. A carotid artery was exposed and cannulated with an intraveinous catheter (type 3F with pink luer fitting, Portex UK) for the measurement of arterial blood pressure via a physiological pressure transducer

(type P23XL, Spectramed USA). To prevent clotting of blood in the arterial cannula the catheter was filled with saline containing heparin (lithium heparin, 50U.ml^{-1} v/v). Blood pressure and tracheal inflation pressure were recorded on a thermal array chart recorder (type TA4000, Gould Electronics UK).

Propranolol (1mg.kg^{-1} i.v. & 3mg.kg^{-1} s.c. Sigma Chemical Co. UK) was administered 10 minutes before PAF in order to prevent the bronchodilatory activity of catecholamines which may be released in response to PAF administration. PAF (100ng.kg^{-1} i.v. bolus) was administered at the one hour time point following oral administration of the test compound or vehicle.

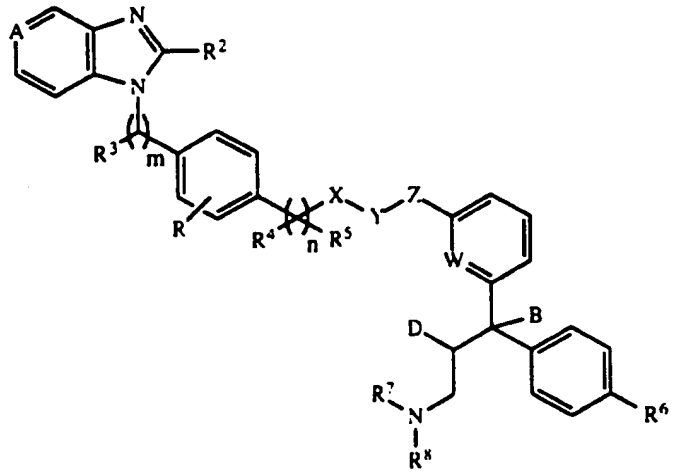
Changes in tracheal inflation pressure and blood pressure of drug treated animals were compared with changes from vehicle treated animals and percentage inhibition determined. One dose of test compound was investigated per animal.

Results

Example	%Inhibition at 10mg/kg *po*
1	42

Claims:

1. A compound of formula (I)



(I)

wherein

A represents =N- or =CR1-, wherein R1 represents hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, halogen, -CN, -CO_2H, -CO_2(C_1-C_6 alkyl), -$CONH_2$, -CHO, -CH_2OH, -CF_3, C_1-C_6 alkoxy, C_1-C_6 alkylsulphanyl, C_1-C_6 alkylsulphinyl, C_1-C_6 alkylsulphonyl, -NH_2, -$NHCOCH_3$, or -NO_2; provided that when A represents =N- the resulting imidazo[4,5-c]pyridinyl bicyclic ring system may be optionally substituted in the 4- and/or 6-positions by methyl;

R represents hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, halogen or C_1-C_6 alkoxy;

R2 represents hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_1-C_6 alkoxy, C_1-C_6 alkylsulphanyl, cyclopropyl, C_1-C_6 hydroxyalkyl, N(C_1-C_6 alkyl)$_2$, C_1-C_6 N(C_1-C_6 alkyl)$_2$ and -CF_3;

R^3 represents hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, -CO_2(C_1-C_6 alkyl), C_1-C_6 alkoxy, C_1-C_6 alkylsulphanyl, (C_1-C_6 alkoxy)C_1-C_6 alkyl, (C_1-C_6 alkylsulphanyl)C_1-C_6 alkyl, (phenyl)C_1-C_6 alkyl, or phenylsulphanyl;

R^4 and R^5 independently represent hydrogen or C_1-C_6 alkyl; or R^4 and R^5 taken together with the carbon atom to which they are attached form a 3-8 membered carbocyclic or heterocyclic ring;

X represents -O-, -S- or -N(R^9)- where R^9 represents hydrogen, C_1-C_6 alkyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl optionally substituted in the cycloalkyl ring with one or more C_1-C_6 alkyl groups, HOOC-(C_1-C_6 alkyl) and ester and amide derivatives thereof, hydroxy(C_1-C_6 alkyl) or C_1-C_6 alkyloxy(C_1-C_6 alkyl);

Y represents a carbonyl or sulphonyl group;

Z represents bivalent C_1-C_6 alkyl, C_2-C_6 alkenyl or C_2-C_6 alkynyl group, or a single bond;

W represents -N= or -CH=;

B represents hydrogen or hydroxyl and D represents hydrogen, or B and D taken together represent -C=C-;

R^6 represents hydrogen, halogen, hydroxy, cyano, C_1-C_4 alkyl, trifluoromethyl, or C_1-C_4 alkyloxy;

R^7 and R^8 independently represent hydrogen or C_1-C_4 alkyl, or R^7 and R^8 taken together with the nitrogen atom to which they are attached form a heterocyclic ring containing 4-7 ring atoms, which ring may contain one or more heteroatoms other than the nitrogen to which R7 and R8

are attached; and

n and m independently represent 0 or 1;

or a pharmaceutically or veterinarily acceptable acid addition salt or hydrate thereof.

2. A compound as claimed in claim 1 wherein A represents =N- .

3. A compound as claimed in claim 1 or claim 2 wherein R represents hydrogen.

4. A compound as claimed in any one of the preceding claims wherein R^2 represents methyl;

5. A compound as claimed in any one of the preceding claims wherein R^3 represents hydrogen;

6. A compound as claimed in any one of the preceding claims wherein R^4 and R^5 independently represent hydrogen or C_1-C_6 alkyl.

7. A compound as claimed in claim 6 wherein both R^4 and R^5 represent hydrogen, or R^4 represents hydrogen and R^5 represents methyl.

8. A compound as claimed in any one of the preceding claims wherein X represents -O- or -N(R^9)-, where R^9 represents hydrogen, methyl or cyclohexyl.

9. A compound as claimed in any one of the preceding claims wherein Y represents carbonyl.

10. A compound as claimed in any one of the preceding claims wherein Z

represents ethyl or E-ethenyl.

11. A compound as claimed in any one of the preceding claims wherein W represents -N=.

12. A compound as claimed in any one of the preceding claims wherein B and D taken together represent -C=C-.

13. A compound as claimed in claim 12 wherein the double bond has E-stereochemistry.

14. A compound as claimed in any one of the preceding claims wherein R^6 represents methyl.

15. A compound as claimed in any one of the preceding claims wherein R^7 and R^8 are independently C_1-C_4 alkyl or taken together with the nitrogen atom to which they are attached form a a pyrrolidine ring.

16. A compound as claimed in any one of the preceding claims wherein n and m both represent 1.

17. A compound selected from the group consisting of:

3-[6-(3-Pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylic acid 4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl ester,

N-[4-(1H-2-Methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]-3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylamide,

N-[4-(1H-2-Methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]-3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-propionylamide,

N-[4-(1H-2-Methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]-3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-propyl)-pyridin-2-yl]-propionate,

3-[6-(3-Pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylic acid 1-[4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-phenyl]-ethylester,

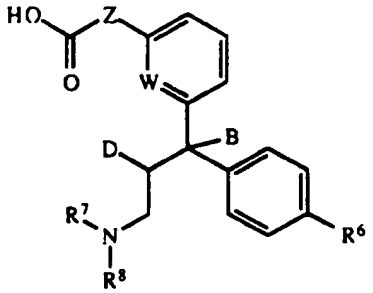
N-Methyl-N-[4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]-3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylamide,

N-Cyclohexyl-N-[4-(1H-2-methyl-imidazo[4,5-c]pyridin-1-ylmethyl)-benzyl]-3-[6-(3-pyrrolidin-1-yl-1-{4-tolyl}-prop-(E)-enyl)-pyridin-2-yl]-acrylamide

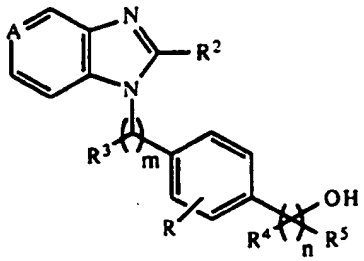
and pharmaceutically and veterinarily acceptable acid addition salts or hydrates thereof.

18. A process for the preparation of a compound as claimed in claim 1 comprising:

(a) (in the case of compounds in which X represents O, and Y represents CO) esterification of an acid of formula (II) with an alcohol of formula (III).



(II)

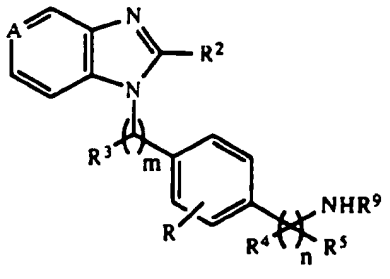


(III)

wherein R, R^2, R^3, R^4, R^5, R^6, R^7, R^8, W, Z, m, n, A, B and D are as defined in formula

(I); or

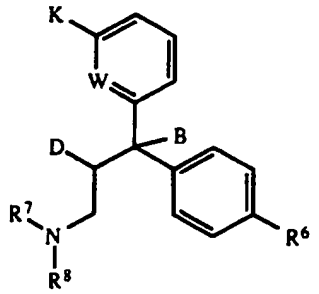
(b) (in the case of compounds in which X represents NR^9 and Y represents CO) amidation of an acid of formula (II) above with an amine of formula (IV):



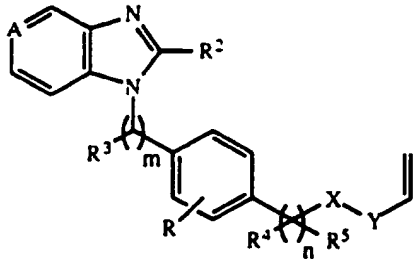
(IV)

wherein R, R^2, R^3, R^4, R^5, R^9, Z, m, n, A are as defined in formula I; or

(c) (in the case of compounds in which Z represents an alkenyl group) palladium catalysed cross coupling reaction between a halide of formula (V) and an alkenyl compound of formula (VI):



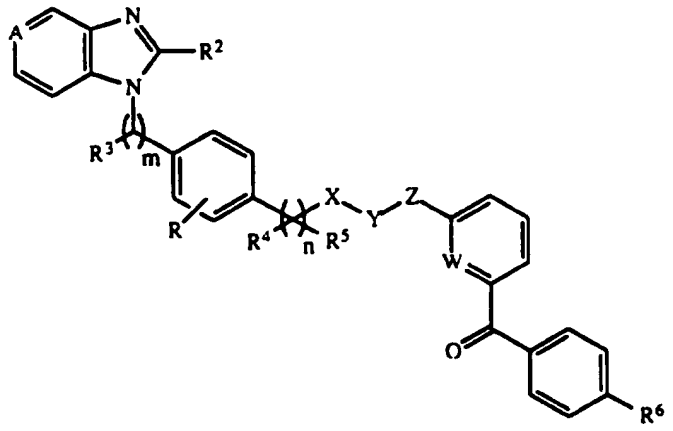
(V)



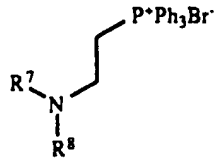
(VI)

wherein R, R^2, R^3, R^4, R^5, R^6, R^7, R^8, W, X, Y, m, n, A, B and D are as defined in formula (I) and K represents a halide; or

(d) (in the case of compounds in which B and D taken together represent -C=C-) the Wittig reaction between a ketone of formula (VII) and a phosphonium salt of formula (VIII)



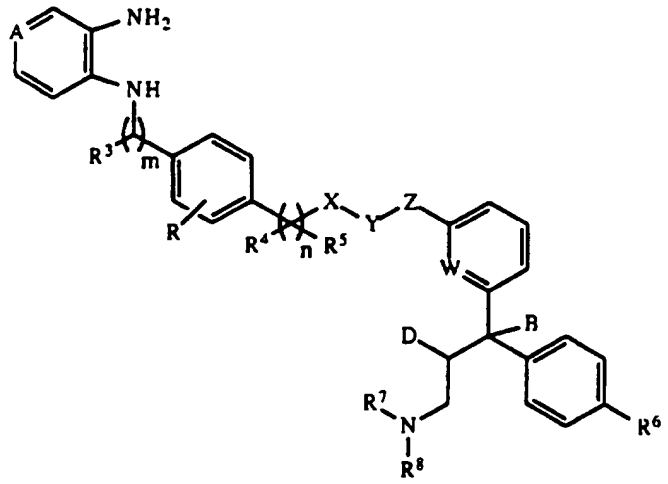
(VII)



(VIII)

wherein R, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, W, X, Y, Z, m, n, and A are as defined in formula I; or

(e) reaction of a diamino compound of formula (IX), with an acid of formula (X) or an activated derivative thereof



(IX)

(X)

wherein R, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, W, X, Y, Z, m, n, A, B and D are as defined in formula I.

19. A method of management of diseases or conditions mediated by histamine and/or PAF in mammals, in particular in humans, which method comprises administering to the mammal an effective amount of a compound as claimed in any of claims 1 to 17, or a pharmaceutically or veterinarily acceptable salt thereof.

20 A compound as claimed in any of claims 1 to 17, or a pharmaceutically or veterinarily acceptable salt thereof, for use in human or veterinary medicine, particularly in the management of diseases or conditions mediated by histamine and/or PAF.

21. The use of a compound as claimed in any of claims 1 to 17, or a pharmaceutically or veterinarily acceptable salt thereof, in the preparation of an agent for the management (by which is meant treatment or prophylaxis) of diseases or conditions mediated by histamine and/or PAF.

22. A method as claimed in claim 19, a compound for use as claimed in claim 20, or the use as claimed in claim 21, wherein the disease or condition is hypotension, thrombocytopenia, bronchoconstriction, circulatory shock, increased vascular permeability (oedema/erythema), allergic rhinitis, sinusitis, asthma, dermatitis, psoriasis, urticaria, anaphylactic shock, conjunctivitis, pruritis, inflammatory bowel disease or colitis.

23. A pharmaceutical or veterinary formulation comprising a compound as claimed in any of claims 1 to 17 and a pharmaceutically and/or veterinarily acceptable carrier.

INTERNATIONAL SEARCH REPORT

Inter. al Application No
PCT/GB 96/00680

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/04 A61K31/415 A61K31/44 C07D213/56 C07D213/55
//(C07D471/04,235:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO,A,92 14734 (PFIZER LTD ;PFIZER (US)) 3 September 1992 cited in the application see the whole document ---	1-18,20, 21,23
Y	WO,A,93 16075 (BRITISH BIO TECHNOLOGY) 19 August 1993 cited in the application see the whole document ---	1-18,20, 21,23
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Y	WO,A,92 03423 (BRITISH BIO TECHNOLOGY) 5 March 1992 cited in the application see the whole document --- -/--	1-18,20, 21,23

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 July 1996	16. 08. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Stellmach, J

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INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/GB 96/00680

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	BIOORG.&MED.CHEM.LETT., vol. 2, no. 6, 1992, OXFORD, pages 597-602, XP002008690 HODGKIN,.E.E. ET AL: "A Partial Pharmacophore for the Platelet Activiating Factor (PAF)" * see page 598, fig .1 *	1-18,20, 21,23
Y	J.COMP.-AIDED MOL.DES., vol. 7, no. 5, October 1993, pages 515-534, XP002008691 HODGKIN,E.E. ET AL.: "A Monte Carlo Pharmacophore Generation Procedure : Application to the Human PAF Receptor " * see page 516, fig. 1 * see the whole document	1-18,20, 21,23
A	WO,A,90 09997 (BRITISH BIO TECHNOLOGY) 7 September 1990 see the whole document	1-18,20, 21,23
A	EP,A,0 260 613 (SEARLE & CO) 23 March 1988 see the whole document	1-18,20, 21,23
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2

INTERNATIONAL SEARCH REPORT

Inte ional application No.
PCT/GB96/00680

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Formula I in claim 1 contains only a minor fixed part, which is not sufficiently limited by claim 2. Considering the large number of variables, the scope of said claims cannot be evaluated and an exhaustive search is not possible. Claims searched incompl.: 1-15,17,18,20,21,23
Claim 22 has not been searched.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/GB 96/00680

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Int ional Application No
PCT/GB 96/00680

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Int. ional Application No
PCT/GB 96/00680

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